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May 4, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Guidance for Industry
ANDAs: Impurities in Drug Products

Docket No. 98D-1168

Dear Colleague:

Baxter Healthcare Corporation is submitting comments on the draft Guidance for Industry: ANDAs: Impurities in Drug Products, released for comment on January 5, 1999.

General Comments

Since the intent of an ANDA is to support the equivalence of the proposed generic drug product to that of the Reference Listed Drug (RLD), we contend that the degradation profile of the proposed generic should not need identification, reporting or qualification independent of the RLD. We therefore recommend that a chromatographic or other appropriate degradation profile comparison to the RLD should be the primary basis to demonstrate equivalence and acceptability of the generic degradation profile. Only in cases where new degradation products or substantially (more than two times the level in the RLD) greater levels of degradation products are present in the generic product, should identification, reporting, and qualification activities, as appropriate, be required.

We found the organization of topics within the document led to confusion and great diversity of interpretation. We recommend that the guidance be organized such that it tracks the chronology of the process. We recommend the following outline:

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I. Introduction
II. Classification
III. Analytical Procedures
IV. Reporting and Identification of Impurities
V. New Impurities
VI. Qualifying Impurities
VII. Acceptance Criteria for Impurities
VIII. Reporting Impurity Contents in Batches

Introduction

Lines 25-27 — We ask that the applicability of this document be limited to significant changes in the formulation, container closure, or the drug substance(s) where equivalency of the drug substances could not be demonstrated. Moreover, the requirements of this document should only apply where these requirements were in force and met by the original ANDA. Degradation product identification and qualification should not be required retrospectively for products currently marketed or for changes where degradation pathways are unaffected.

Classification — Please clarify the definition of unspecified degradation products.

Identifying and Reporting Impurities

We feel that it would be clearer to present the requirements for analytical procedures (currently section IV) before discussing the requirements around reporting of impurities.

Lines 63-69 — We question the value of discussing degradation pathways common to both the generic and RLD. We contend that only differences (as defined in 225-228) from the RLD need be explained.

Lines 76-78 — The sentence beginning in line 76 should be revised as follows: "Degradation products ...should be reported and identified...in Attachment A, Table 1 or Table 2 are equaled or exceeded." This sentence should be included in the opening paragraph of section III, preceding lines

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63-69 so that thresholds for reporting and identification are identified up front.

Lines 87-99 — We recommend that the chromatographic degradation profile comparison (Lines 211 – 234) should be the primary basis to demonstrate equivalence of degradation products in the generic and the RLD. Only in cases where the generic contains new degradation products above the threshold, or substantially (2X) greater levels than in the RLD should preparation of standards and identification be required.

Analytical Procedures

This section should precede section III (i.e., Identifying and Reporting Impurities).

Lines 101-102 — We feel that it is important in this section to clearly state the expected detection and quantitation capabilities of the analytical procedures. Therefore, we recommend that the threshold levels for reporting be referenced here.

Lines 110 – 117 — We contend that since the critical comparison is to the RLD, the actual response factor of each degradation product is only relevant when both substantial differences to the RLD are observed and qualification thresholds may be exceeded. A quantitative comparison can accurately be made with the RLD for unidentified degradation products without knowledge of the response factor, as the response factor should be the same in the RLD and the proposed generic.

Reporting Impurity Contents in Batches

This section provides good closure and summary of this guidance; therefore, it should follow Acceptance Criteria for Impurities.

Line 140 — We request that for unidentified degradation products, it be acknowledged that reporting of total degradation products and largest unidentified individual degradation

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product is sufficient. This provides adequate control of product quality and ongoing monitoring as these degradation products are necessarily below the identification threshold and encompassed in the reporting of total degradation products.

Acceptance Criteria for Impurities

It appears that generic products are being held to a higher standard than their RLD. We question the value of this approach. For example, lines 146-147 requires all ANDAs to include acceptance criteria for degradation products expected to occur under recommended storage conditions. This requirement should only apply to those degradation products, which are different or exceed two times the level present in the RLD.

Lines 161-162 — It should be acceptable to control all unidentified degradation products by reporting only the largest unidentified degradation product. In this manner, all unidentified degradation products are necessarily below the threshold for identification and therefore are adequately controlled without the burden of individual reporting and acceptance criteria.

Qualifying Impurities

Qualification Procedures

Lines 225-234 — Unidentified, as well as identified, degradation products should be qualified through a comparison to the RLD. Therefore, please remove the term "identified" from line 226 and "unidentified and" from line 233. This is justified since the thresholds for identification necessarily control the levels of unidentified degradation products and the comparability to the RLD assures previous qualification.

Decision Tree — We propose that only those degradation products, which are unique to the proposed generic or are at substantially (2X) greater levels than the RLD be considered for identification, reporting, and

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	considered for identification, reporting, and qualification. Therefore, we recommend that an initial comparative screen is conducted prior to entering the First Level (L1) of the Decision Tree (lines 262-264 and Attachment B).
Lines 254-256	The use of the Decision Tree should only apply to degradation products which are unique to the proposed generic or at substantially (2X) greater levels than the RLD. This simplifies preparation and review of submissions without exposure of the public to any new or higher levels of degradation products.
Attachment B	A statement should be added to this decision tree to clarify that it is for the qualification of degradation products that are unique to the proposed generic or in substantially (2X) greater quantity than the RLD.

We appreciate the opportunity to comment on this draft guidance. If you have any questions regarding our comments, please contact me. We are open to follow-up discussions on these comments and would be willing to meet with the Agency to facilitate discussions if appropriate.

Sincerely,

Marcia Marconi
Vice President
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